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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/664,037

09/17/2003

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P-6186

2610

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7590

05/30/2008

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EXAMINER

AFRIMOVA, VERA

ART UNIT

PAPER NUMBER

1657

MAIL DATE

DELIVERY MODE

05/30/2008

PAPER

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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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*Ex parte* RICHARD D. GUARINO, SHARON C. PRESNELL,  
ANDREA LIEBMANN-VINSON, and MOHAMMAD A. HEIDARAN

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Appeal 2008-2151  
Application 10/664,037  
Technology Center 1600

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Decided: May 30, 2008

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Before DONALD E. ADAMS, LORA M. GREEN and  
FRANCISCO C. PRATS, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1-3, 6-8, 10, 12-16, 58, and 61-67. We have jurisdiction under 35 U.S.C. § 6(b). Claims 1 and 58 are representative of the claims on appeal, and read as follows:

1. A method for culturing primary liver cells comprising:

(a) providing a polymer composition comprising a CAR material, and one or more ECM proteins and a polycationic polymer bound to said CAR material, wherein said CAR material, said one or more ECM proteins, and said polycationic polymer thereby form a cell adhesion promoting surface; and

(b) incubating said liver cells in the presence of said surface in a medium that supports growth and/or maintenance of said liver cells, such that said liver cells attach to the surface;  
thereby culturing said liver cells.

58. A method for culturing primary liver cells comprising:

(a) providing a polymer composition comprising a CAR material, and collagen I and poly-L-ornithine bound to said CAR material, wherein said CAR material, collagen I and poly-L-ornithine thereby form a cell adhesion promoting surface; and

(b) incubating said liver cells in the presence of said surface in a medium that supports growth and/or maintenance of said liver cells, such that said liver cells attach to said surface;  
thereby culturing said liver cells.

The Examiner relies on the following references:

Dunn	US 5,942,436	Aug. 24, 1999
Toner	US 6,562,616 B1	May 13, 2003
Triglia	US 6,653,105 B2	Nov. 25, 2003
Fukuda (English Abstract)	JP 04322657	Nov. 12, 1992
Abatangelo	WO 98/56897	Dec. 17, 1998

We affirm.

## DISCUSSION

Claims 1-3, 6-8, 10, 12-16, 58, and 61-67 stand rejected under

35 U.S.C. § 103(a) as being obvious over the combination of Abatangelo, Toner, Dunn, Triglia, and Fukuda. We focus our analysis on claim 1, and as Appellants have not argued claims 2, 3, 6-8, 12-16, and 61-64 separately, they stand or fall with claim 1. 37 C.F.R. § 41.37(c)(1)(vii).

Abatangelo, Toner, and Dunn are all cited for teaching “methods for culturing mammalian liver cells including rat and human liver cells attached to ECM proteins such as collagen type I that is coated on/bound to non-adhesive (CAR) materials including HA.” (Ans. 5) According to the Examiner, the references “are lacking particular disclosure about the use of polycationic polymer or poly-L-ornithine in the surface coating composition in the method for culturing liver cells.” (*Id.* at 6.)

Triglia and Fukuda are cited to make up that deficiency. Specifically, Triglia is cited for teaching “methods for culturing mammalian liver cells including human hepatocytes (col. 4, line 6) and suggests the use of attachment surfaces that are composed of poly-ornithine and collagen as suitable compositions for attachment, incubating and growing hepatocytes (col. 6, lines 5-24).” (Ans. 6.) Fukuda is then cited for suggesting “culturing liver cells in the presence of biologically active composition such as a mixture of materials selected from collagen, poly-L-ornithine, glasses, organic polymers and or silicone-based rubbers.” (Ans. 6.)

The Examiner concludes that

it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to add poly-L-ornithine taught by [Triglia and Fukuda] to the coating polymer compositions of [Abatangelo, Toner, and/or Dunn] with a reasonable expectation of success in culturing liver cells because the cell attachment surfaces comprising poly-L-ornithine and collagen type I have been taught and/or suggested

by the prior art of attaching, incubating and growing hepatocytes as adequately demonstrated by the cited reference[s] combined.

(Ans. 6.)

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court has recently emphasized that “the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR Int’l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). “The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *Id.* at 1739. Moreover, an “[e]xpress suggestion to substitute one equivalent for another need not be present to render such substitution obvious.” *In re Fout*, 675 F.2d 297, 301 (CCPA 1982).

We conclude that the Examiner has set forth a prima facie case of obviousness. We thus turn to Appellants’ arguments in rebuttal.

Appellants argue that there is no motivation to combine the references as suggested by the Examiner (App. Br. 9). Appellants, citing *KSR*, acknowledge that the United States Supreme Court “declined to permit a ‘rigid’ application of the teaching-suggestion-motivation to combine test to obviousness determinations,” but argue that the Court also held that “the

presence or absence of a teaching, suggestion or motivation to combine the cited references provides a ‘helpful insight’ regarding the obviousness of an invention.” (R. Br. 3, citing *KSR*, 127 S. Ct. at 1731.) In this case, Appellants assert, no such “helpful insight” exists (R. Br. 3).

As to Triglia, Appellants argue that the reference is drawn to serum-free C3A cells, which are not primary liver cells, asserting as it “is well known to one of ordinary skill in the art, the requirements for culturing primary liver cells are significantly different from those required for culturing an established hepatocyte line.” (*Id.*) As to Fukuda, Appellants argue that the reference is drawn to “a cell culture surface having fine protrusions and grooves and coated with one or a mixture of collagen, poly-L-lysine, poly-L-ornithine, laminin, fibronectin, chick plasma, artificial lipid films, and nerve growth factors, can be used to culture cells and tissues including connective tissues and nerve, glia, Schwann, skin, muscle, kidney, and liver cells,” asserting that “general statements that one or a mixture of poly-L-ornithine, poly-L-lysine, laminin, collagen, fibronectin, chick plasma, artificial lipid films, and nerve growth factors may be used in culturing various cell types do not guide the skilled artisan in arriving at Appellants’ specific methods for culturing primary liver cells.” (App. Br. 9.) At best, Appellants assert, the combined teachings only rise to the level of an invitation to experiment, and do not render the claimed invention obvious (*id.*).

Appellants argue further that the Court in *KSR* acknowledged the importance in identifying a reason that would have led the ordinary artisan in the relevant field to make the combination (R. Br. 4, citing *KSR*, 127 S. Ct. at 1731). Here, Appellants assert, the Examiner has attempted to piece

together five references that teach various elements of the claims, wherein the references “are directed to the culturing of various cells and tissues on a variety of surfaces in the presence of various substances.” Thus, Appellants assert, the Examiner has engaged in impermissible hindsight in formulating the rejection (*id.*).

Appellants’ arguments have been considered, but are not convincing. Each of Abatangelo, Toner, and Dunn were cited for teaching methods for culturing primary mammalian liver cells including rat and human liver cells attached to ECM proteins such as collagen type I that is coated on/bound to non-adhesive (CAR) materials, including HA (Ans. 5), and Appellants do not dispute that factual finding of the Examiner. Those references only failed to teach a single element, the addition of a polycationic polymer—such as poly-L-ornithine—to the cell adhesion surface.

Triglia and Fukuda were cited to make up that deficiency. As to Triglia, we agree with Appellants that the reference is drawn to culturing a C3A, which is a cell line derived from liver (hepatocyte) cells (Triglia, col. 4, ll. 3-10). The cell line, however, “mimic[s] both qualitatively and quantitatively liver cells or the liver as a functioning organ,” “synthesize near normal levels of albumin and other proteins,” and “exhibit the structure and polarity characteristic of normal human hepatocytes.” (Triglia, col. 4, ll. 10-20). According to Triglia, appropriate attachment of spreading surfaces by selecting and treating suitable surfaces, with “[c]ommon treatments [being] well known and include coating surfaces with compositions . . . [that] are also well known and include polybasic amino acids such as polyornithine and polylysine.” (Triglia, col. 6, ll. 12-16.) The surface may

also be provided with an extracellular matrix protein such as collagen and fibronectin (*id.* at ll. 23-26).

Fukuda teaches the culture of primary liver cells (English Abstract; *see also*, Translation, p. 10, Practical Example 4). Specifically, Fukuda teaches that a biologically active substance is attached to the culturing surface, and includes one of a mixture of collagen, poly-L-lysine, poly-L-ornithine, laminin, fibronectin, tick plasma, artificial lipid films, and nerve growth factors (*id.*).

Thus, both Fukada and Triglia teach the use of a polycationic polymer such as poly-L-ornithine or poly-L-lysine with collagen for the attachment of a liver cell, and in the absence of unexpected results, it would have been obvious to the ordinary artisan at the time of invention to add it to the culture surfaces of Abatangelo, Toner, and Dunn, because all the references teach culture of liver cells. Thus, the Examiner has clearly identified a reason for combining the references, and such a combination does not amount to impermissible hindsight. As noted by the United States Supreme Court,

If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.

*KSR*, 127 S. Ct. at 1740.

As to the argument that Triglia is drawn to the culture of C3A cells, and that it is well known that the requirements for culturing primary liver cells are significantly different from those required for culturing an



established hepatocyte line; Appellants provide no evidence to that effect, and arguments of counsel cannot take the place of evidence in the record. *In re Scarbrough*, 500 F.2d 560, 566 (CCPA 1974). Moreover, the Specification teaches that one way that the cultured liver cells maintain function is that they produce albumin (Spec. 2). As Triglia teaches that the C3A cell line produces albumin, as well as mimicking both qualitatively and quantitatively liver cells or the liver as a functioning organ, the ordinary artisan would have had a reasonable expectation of success of adding polylysine or polyornithine as taught by Triglia to the culture surfaces of Abatangelo, Toner, and Dunn and have successful culture of primary liver cells. Finally, Fukada teaches the use of poly-L-lysine or poly-L-ornithine in the culture of primary liver cells, thus also providing a reasonable expectation of success.

As to claims 10, 58, and 65-67, Appellants argue that the claims contain limitations that collagen I and poly-L-ornithine be bound to the CAR material, and are thus more narrow in scope (App. Br. 10-11). Specifically, Appellants argue that the combination does “not guide the skilled artisan in arriving at Appellants’ specific method for culturing primary liver cells, comprising providing a cell adhesion promoting surface including a CAR material, collagen I and poly-L-ornithine,” but merely invite experimentation (*id.* at 11).

Triglia specifically teaches the use of polyornithine and polylysine, and Fukada teaches the use of poly-L-lysine or poly-L-ornithine, thus it would have been obvious to use poly-L-ornithine as part of the cell culture surface in the culture of primary liver cells. As to the use of collagen I, all of the references teach the use of collagen, and the addition of any collagen,

including collagen I, would have been prima facie obvious to the ordinary artisan in the absence of unexpected results. Moreover, as noted by the Examiner (Ans. ), both Toner and Dunn specifically teach the use of collagen I (*see, e.g.*, Dunn, col. 4, ll. 43-46), demonstrating that its use in a cell culture attachment surface in the culturing of primary liver cells was known to the ordinary artisan.

### CONCLUSION

In summary, because we find that the Examiner has set forth a prima facie case of obviousness as to all of the claims, the rejection of claims 1-3, 6-8, 10, 12-16, 58, and 61-67 under 35 U.S.C. § 103(a) as being obvious over the combination of Abatangelo, Toner, Dunn, Triglia, and Fukuda, is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

### AFFIRMED

dm

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